## REMARKS

Upon entry of the amendments and new claim, claims 2-33, and 38 will be pending.

Claims 1 and 34-37 have been cancelled herein without prejudice or disclaimer, and Applicants expressly reserve the right to pursue the subject matter in a related application.

Claims 2, 4-10, 12-17, 21-27, 29, and 31 have been amended herein. The amendments have been made in order to clarify the subject matter regarded as the invention and are supported by the claims as originally filed and throughout the specification (see, e.g., paragraphs 00033, 00034, 00046, 00048). As such, the amendments to the claims do not add new matter.

### Objection to the Claims

The Examiner has objected to claim 5 as informally containing acronyms "COIN" and "SERS" that are not defined in the claims in their entirety. Claim 5 has been amended to fully recite a "composite organic-inorganic nanoparticle (COIN)" and "surface enhanced Raman spectroscopy (SERS)". Accordingly, withdrawal of the objection is respectfully requested.

### Rejections Under 35 U.S.C. § 112

The rejection of claims 1-33 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention is respectfully traversed. Applicants initially point out that the amendments to the claims herein include cancellation of claim 1 and addition of new claim 38. As such, the rejections will be addressed as they apply to the currently presented claims.

It is alleged that part a) of claim 1 is indefinite because it is unclear how the proteins are separated on the basis of chemical and/or physical properties. It is further alleged that the claim

is unclear as to whether the proteins are separated from proteins that are dissimilar in chemical and/or physical properties or if the sample is separated into smaller samples with any chemical and/or physical properties. Claim 1 has been cancelled and new claim 38 clarifies that that the claimed methods include chromatographically separating proteins and protein fragments in the sample into a plurality of fractions. Applicants submit that the skilled artisan would recognize that chromatographically separating proteins includes separating proteins with similar chemical and/or physical properties from those proteins having dissimilar chemical and/or physical properties (see, e.g., paragraph 00034).

It is further alleged that claim 1 is indefinite because part b) of claim 1 is unclear as to whether separated proteins are maintained in a separated state are the same proteins of part a). It is further alleged, with regard to part b), that claim 1 is unclear as to whether the proteins are deposited onto a solid substrate. It is further alleged that claim 1 is unclear as to how the proteins are separated within a stream of flowing liquid and if there is more than one stream of flowing liquid to perform maintenance of protein separation. Claim 1 has been cancelled and claim 38 clarifies that the inventive method includes depositing each fraction at a discrete location on a solid substrate or within at least one stream of flowing liquid in a microfluidic system to create a plurality of discrete protein enriched locations, thereby maintaining the chromatographically separated proteins and protein fragments in a separated state.

It is also stated in the Office action that claim 1 includes multiple parts labeled as part c) and it is unclear whether those parts are intended to be a single step. Applicants point out that this typographical error has been corrected by the present amendment including cancellation of claim 1.

It is further alleged in the Office action that claim 1 is unclear as to how structural information is provided by the Raman spectra. Claim 38 corrects the alleged lack of clarity of claim 1 and provides that a Raman spectrum at a discrete protein enriched location provides

information about the chemical composition of a protein deposited at the corresponding discrete protein enriched location.

It is alleged that claim 2 is vague because it is unclear what information regarding source of the sample is correlated with information of the Raman spectra. Claim 2 has been amended to recite that the inventive methods include further comprising correlating the information with information about a patient from which the sample is obtained (see, e.g., paragraph 00046).

It is further alleged that claim 7 is unclear as to whether denaturing proteins includes contacting proteins with a denaturing agent. Claim 7 has been amended to clarify the subject matter regarded as the invention.

It is further alleged in the Office action that claim 23 is indefinite because it is unclear what relation is correlated between the SERS spectra and the sample locations. Claim 23 has been amended to clarify that Raman spectra and locations of the proteins on the solid substrate or within the at least one stream of flowing liquid are recorded and correlated, thereby clarifying the claimed subject matter.

It is further alleged that claims 25 and 26 are unclear, for example, as to how the proteins are maintained in a separated state, whether the proteins are separated within the same stream, and, with regard to claim 26, how the stream of separated proteins mixes with a stream of metal colloids. Claims 25 and 26 have been amended to clarify the subject matter regarded as the invention. Applicants submit that methods of combining two streams of liquid within a microfluidic system, such that the contents of the streams are combined and in contact with each other, could easily be envisioned by those of skill, such that the skilled artisan would recognize the metes and bounds of the claimed subject matter.

It is further alleged that claim 1 is indefinite because the limitation "the protein content" lacks antecedent basis. As noted above, claim 1 has been cancelled. Applicants submit that new claim 38 corrects the ambiguity pointed out by the Examiner.

It is further pointed out that the term "the denaturing agent" in claim 7 lacks antecedent basis. Because the cited term is not present in originally filed claim 7, Applicants believe that the Examiner's rejection is, in fact, directed to claim 8. Nevertheless, claims 7 and 8 have been amended to provide the proper antecedent basis for the term "the denaturing agent" as recited in claim 8.

**Rejection Under 35 U.S.C. § 102**

The rejection of claims 1-5, 10, 14-17, 20-26 and 29-33 under 35 U.S.C. § 102(e) as being anticipated by Natan et al. (U.S. Patent No. 6,579,721) is respectfully traversed. The amendments to the claims herein include cancellation of claim 1 and addition of new claim 38. As such, the rejections will be addressed as they apply to the currently presented claims.

A rejection of claims under 35 U.S.C. § 102 is improper unless each and every element of the claimed subject matter is found, either expressly or inherently, in a single prior art reference (*Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP § 2131). The currently claimed method for analyzing protein content of a complex biological sample includes a) chromatographically separating proteins and protein fragments in the sample into a plurality of fractions, each fraction containing an individual protein or protein fragment; b) depositing each fraction at a discrete location on a solid substrate or within at least one stream of flowing liquid in a microfluidic system to create a plurality of discrete protein enriched locations, thereby maintaining the chromatographically separated proteins and protein fragments in a separated state; c) contacting the separated proteins deposited at the plurality of discrete protein enriched locations with capture probes under conditions suitable to form a capture probe/protein complex at one or more of the discrete protein enriched locations; d) contacting the complexes with a Raman-active probe construct that binds to the protein or the complex; and e) detecting Raman spectra produced by the probe construct/protein complexes at the plurality of discrete protein enriched locations, wherein a Raman spectrum at a discrete

protein enriched location provides information about the chemical composition of a protein deposited at the corresponding discrete protein enriched location, thereby analyzing the protein content of a complex biological sample. Applicants submit that those elements of claim 38, which are incorporated into the corresponding dependent claims, are missing from the Natan et al. reference, thereby precluding a finding of anticipation.

In particular, Applicants point out that Natan fails to teach a method that includes chromatographically separating proteins and protein fragments in the sample into a plurality of fractions. The Examiner cites Natan at column 23, lines 45-48 as allegedly teaching separating proteins in a sample on the basis of chemical properties of the protein. The teachings of Natan, however, are limited to physical separation of a sample into smaller portions or allotments, such as by distributing or allotting portions of a sample into individual microwells that are not fluidically connected. Natan contemplates dividing a sample into smaller volume allotments, which are each distributed into an array of microwells for the purpose of conducting separate chemical reactions in the individual microwells. While the samples of Natan are divided into allotments of smaller volume and distributed into individual microwells, the proteins in the sample are not in any way distinguished from each other prior to separation. More specifically, Natan does not contemplate chromatographically separating proteins or protein fragments in a sample into a plurality of fractions, with each fraction containing an individual protein or protein fragment. As such, Applicants submit that the cited reference does not anticipate the currently claimed methods because Natan does not teach each and every element of the claimed invention, including chromatographically separating proteins or protein fragments prior to analysis.

In summary, for the reasons set forth above, it is submitted that the cited reference does not teach each and every element of the claimed invention. Accordingly, removal of the rejection of claims 1-5, 10, 14-17, 20-26 and 29-33 under 35 U.S.C. § 102(e), as allegedly lacking novelty in light of Natan et al., is respectfully requested.

**Rejections Under 35 U.S.C. § 103**

The rejection of claims 6-9 under 35 U.S.C. § 103, as allegedly being unpatentable over Natan et al. (U.S. Patent No. 6,579,721) in view of Grow (U.S. Patent No. 6,040,191), is respectfully traversed.

It is alleged in the Office action that it would have been obvious to a skilled artisan to include in the method for analyzing protein content of a biological sample of Natan, a step of denaturing proteins, as taught by Grow, in order to teach the methods of claims 6-9. As discussed above, however, Natan does not teach a method for analyzing protein content of a biological sample that includes each element of the method as set forth in claim 38, including a method that includes chromatographically separating proteins or protein fragments in a sample into a plurality of fractions, with each fraction containing an individual protein or protein fragment. Since Grow does not provide the teachings that are missing from Natan, it is submitted that the failure of the cited references to teach a method for analyzing protein content of a complex biological sample as claimed remains for the reasons set forth above.

Accordingly, Applicants respectfully request removal of this ground of the rejection.

The rejection of claims 11-13 under 35 U.S.C. § 103, as allegedly being unpatentable over Natan et al. (U.S. Patent No. 6,579,721) in view of Avseenko et al. (Analytical Chemistry, 2001, 73, 6047-6052), is respectfully traversed.

It is alleged in the Office action that it would have been obvious to a skilled artisan to include in the method for analyzing protein content of a biological sample of Natan, the methods of depositing the separated proteins on a solid substrate, including aluminum, as taught by Avseenko, in order to teach the methods of claims 11-13. As discussed above, however, Natan does not teach a method for analyzing protein content of a biological sample that includes each element of the method as set forth in claim 38, including a method that includes

chromatographically separating proteins or protein fragments in a sample into a plurality of fractions, with each fraction containing an individual protein or protein fragment. Since Avseenko does not provide the teachings that are missing from Natan, it is submitted that the failure of the cited references to teach a method for analyzing protein content of a complex biological sample as claimed remains for the reasons set forth above.

Accordingly, Applicants respectfully request removal of this ground of the rejection.

The rejection of claims 18 and 19 under 35 U.S.C. § 103, as allegedly being unpatentable over Natan et al. (U.S. Patent No. 6,579,721) in view of Storhoff et al. (U.S. Pat. Application No. 2004/0053222), is respectfully traversed.

It is alleged in the Office action that it would have been obvious to a skilled artisan to include in the method for analyzing protein content of a biological sample of Natan, enhancer salts, including LiCl, as taught by Storhoff, in order to teach the methods of claims 18 and 19. As discussed above, however, Natan does not teach a method for analyzing protein content of a biological sample that includes each element of the method as set forth in claim 38, including a method that includes chromatographically separating proteins or protein fragments in a sample into a plurality of fractions, with each fraction containing an individual protein or protein fragment. Since Storhoff does not provide the teachings that are missing from Natan, it is submitted that the failure of the cited references to teach a method for analyzing protein content of a complex biological sample as claimed remains for the reasons set forth above.

Accordingly, Applicants respectfully request removal of this ground of the rejection.

The rejection of claims 27 and 28 under 35 U.S.C. § 103, as allegedly being unpatentable over Natan et al. (U.S. Patent No. 6,579,721) in view of Nelson et al. (U.S. Patent No. 5,955,729), is respectfully traversed.

It is alleged in the Office action that it would have been obvious to a skilled artisan to include in the method for analyzing protein content of a biological sample of Natan, surface plasmon resonance-mass spectroscopy, as taught by Nelson, in order to teach the methods of claims 27 and 28. As discussed above, however, Natan does not teach a method for analyzing protein content of a biological sample that includes each element of the method as set forth in claim 38, including a method that includes chromatographically separating proteins or protein fragments in a sample into a plurality of fractions, with each fraction containing an individual protein or protein fragment. Since Nelson does not provide the teachings that are missing from Natan, it is submitted that the failure of the cited references to teach a method for analyzing protein content of a complex biological sample as claimed remains for the reasons set forth above. Accordingly, Applicants respectfully request removal of this ground of the rejection.

Accordingly, for the reasons set forth above, Applicants submit that the claimed invention would not have been obvious in view of the cited references and, therefore, respectfully request that the rejection of the claims under 35 U.S.C. § 103 be removed.

The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application. The Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896.

Respectfully submitted,

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